Obstructive Lung Disease

Introduction

Obstructive lung disease defines a large umbrella of diseases in which airway resistance is increased, compromising the movement of air out of the alveoli. Obstructive lung disease comes down to two main diagnoses: chronic obstructive pulmonary disease in the elderly, and childhood asthma. **Chronic obstructive pulmonary disease** (COPD) is the name of the diagnosis that encompasses both emphysema and bronchitis. COPD is **chronic,** and the destruction **irreversible**. All COPD patients have evidence of both pathologies, and all COPD is treated in the same escalating pattern. But in comprehending the cellular mechanisms of disease, we are going to teach COPD as if there are two, distinct diagnoses. **Bronchitis** is a hypoxemic disease caused by excess mucus secretion in the bronchi and inflammation that fibroses the bronchioles. **Emphysema** is a hypercapnic disease caused by the loss of both elastin and the alveolar septa within the alveolar sacs. Then, off on its own, **asthma** is the name of the diagnosis that encompasses both atopic and nonatopic asthma. Asthma is an **acute** disease characterized by bronchiole smooth muscle cell spasms, called **bronchoconstriction**. Atopic asthma is the asthma that matters, though we will touch on nonatopic causes.

We will progress through chronic bronchitis, then emphysema, and close with asthma.

Chronic Bronchitis

Chronic bronchitis (bronchi-itis) is an inflammatory disease of the **large-caliber bronchi**. The purpose of these early conducting airways is to warm and clean the air as it moves into the smaller airways. That cleaning is achieved by the trapping of pathogens and particles in the air surface liquid (ASL; Pulmonary: Lung #1: *Introduction to Pulmonary*). At the level of the bronchi, the **submucosal glands** are responsible for most of the ASL (along with help from goblet cells in the mucosa). These glands also disappear from the submucosa as the airway branches into bronchioles. Therefore, since chronic bronchitis is a disorder of the large-caliber airways, our focus is on the submucosal glands.

Chronic bronchitis is a **disease of cigarette smoking**. Cigarette smoke has a lot of bad stuff in it—debris, chemicals, irritants, etc. The job of the large conducting airways is to clean the air being inhaled. Intentionally burning and inhaling noxious particles isn't something humans are meant to do. When the burden of cleaning the air is increased dramatically by cigarette smoking, the bronchi respond. The way those noxious particles are cleaned from the air is with mucus. The main source of mucus in the bronchi is the submucosal glands. To make more mucus, there must be more glands. **Submucosal gland hypertrophy** (bigger glands) **and hyperplasia** (more of them) define the histologic basis of the disease. Although the number of goblet cells does increase slightly, the major change is in the number of mucus glands. This increase can be assessed by the ratio of the thickness of the glandular layer to the total thickness of the bronchial wall, from the cartilage to the basement membrane of the epithelium. This ratio is called the **Reid index**. The Reid index is normally 0.4 or less (40% of the thickness is glands) and is increased in chronic bronchitis, usually in proportion to the severity and duration of the disease.

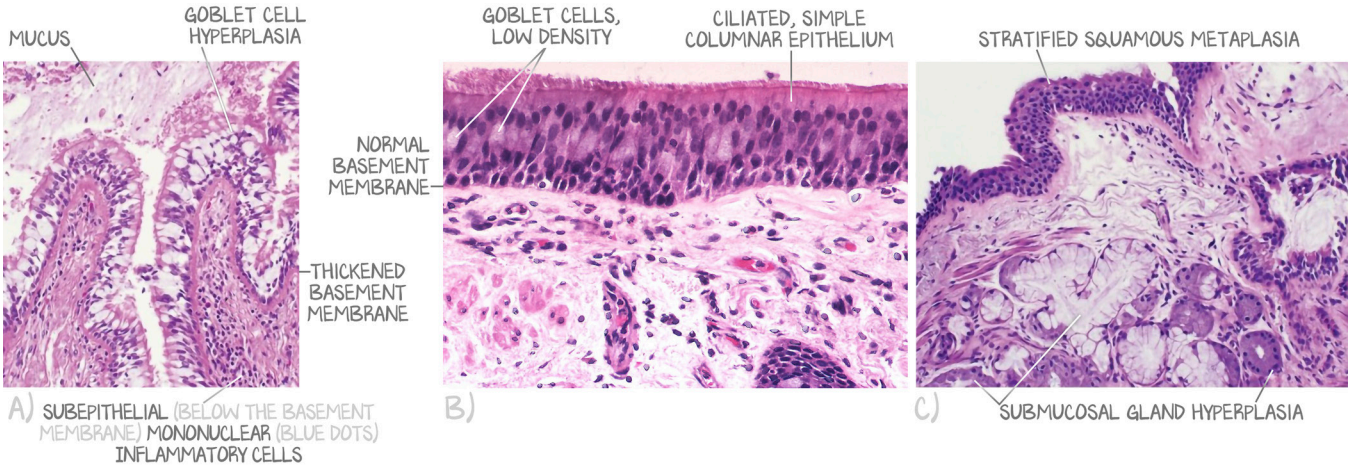


Figure 6.1: Chronic Bronchitis Histology
(a) Section of a bronchiole (distal airway with no submucosal glands) demonstrating the accumulation of mucus, goblet cell hyperplasia—there are way more white cells than in the normal primary bronchus in panel b, basement membrane thickening, and far more nuclei (blue dots) in the lamina propria. (b) Normal bronchiole for comparison, demonstrating pseudostratified columnar (but really it's more simple columnar) epithelium with cilia, a few goblet cells, and no visible submucosal glands. (c) High-power view of the primary bronchus, demonstrating submucosal gland hyperplasia (almost 70% of the submucosa is glands, although you cannot see the entirety of the submucosa) and metaplasia to stratified squamous epithelium.

More mucus is produced to trap more air pollutants. More mucus is secreted into the lumen of the bronchi. That mucus has to go somewhere. The mucociliary escalator drives it up toward the pharynx. Excess mucus that is produced and delivered to the throat presents as a **chronic productive cough**. The diagnosis is made clinically by finding a **persistent cough with sputum production for at least three months in the past two years**, in the absence of any other identifiable cause. Smoker plus chronic productive cough equals chronic bronchitis.

But if the mucus doesn't all come out into the oropharynx, the only other place it has to go is down to the smaller-caliber bronchioles. Smoking exacerbates this, as it also impairs the mucociliary elevator. Excess mucus in the small airways causes **mucus plugging** and prevents air movement. Not being able to get air to the alveoli means not getting oxygen to the alveoli. This causes **hypoxemia**, which presents as **cyanosis** (blue color). Persistent pulmonary hypoxemia causes pulmonary arteriole vasoconstriction, which results in pulmonary hypertension (Pulmonary: Circulation #3: *Pulmonary Hypertension*). Pulmonary hypertension, in turn, induces right heart failure. The signs and symptoms of right heart failure are jugular venous distention and **peripheral edema** (bloaters). In early disease, patients present with a chronic, productive cough. In late disease, patients present with a chronic, productive cough, peripheral edema, and cyanosis, which gives these patients the name ***blue bloaters***, to contrast with the pathophysiology of emphysema.

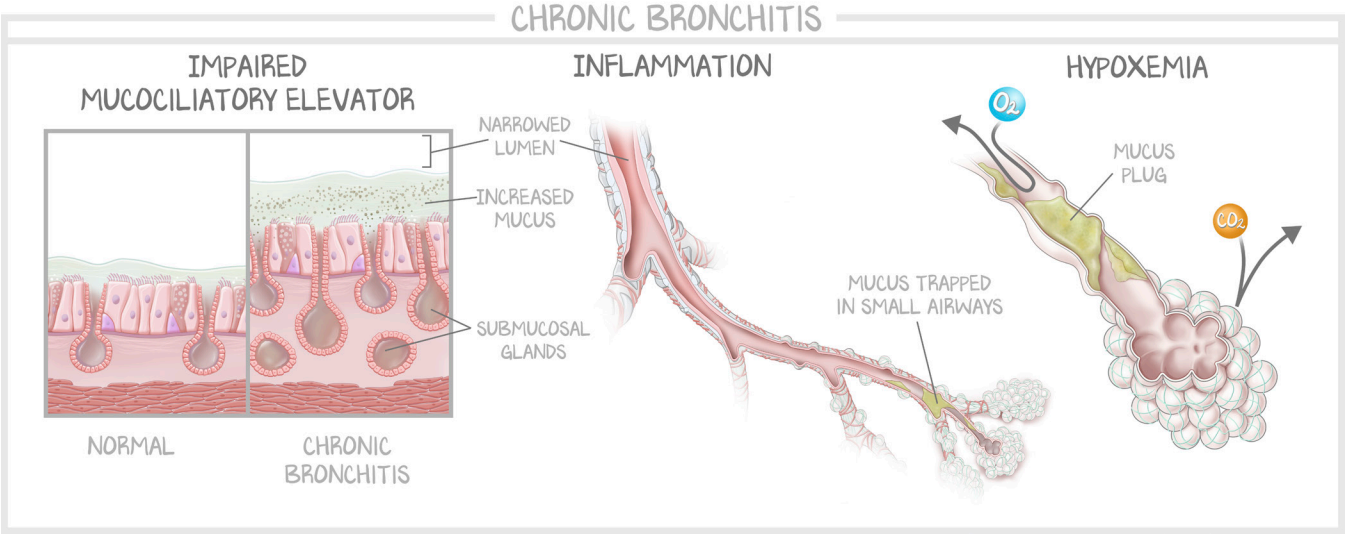


Figure 6.2: Pathogenesis of Chronic Bronchitis
A schematic of the changes that occur in the conducting airways and the respiratory airways. The preliminary insult is felt at the conducting airways, which respond with increases in both the number of submucosal glands and mucus production, which lead to the narrowing of the caliber of the lumen. Increased mucus then descends down the respiratory tree, causing mucus plugging and preventing airflow into and out of alveoli.

Inhalants that induce chronic bronchitis cause epithelial damage, eliciting acute inflammation responses. Neutrophils arrive first, then macrophages, then fibroblasts. Fibroblasts lay down collagen—scar tissue. In small airways, fibrosis leads to the reduction of the caliber of the lumen, and in severe cases, can lead to the obliteration of the lumen. Mucus plugging and fibrosis narrow the lumen of the airway. A decreased airway diameter means increased airflow resistance. Because on inhalation the bronchioles are opened by the tugging of the diaphragm, air is able to get into the alveoli. On exhalation, the air is trapped. All obstructive lung diseases are CO_2 retention diseases. **Hypercapnia**, in addition to the "blue bloater" state of advanced disease, is part of chronic bronchitis. Hypercapnia, just as in the other diseases, is caused by changes in the bronchioles.

Inhalants that induce chronic bronchitis cause epithelial damage, and the epithelium responds with **squamous metaplasia**. Metaplasia is a risk factor for malignant transformation, and thus an increased risk of squamous cell carcinoma of the lung, also justifying why SCC of the lung occurs "sentrally" (Pulmonary: Lung #10: *Lung Cancer*).

Emphysema

Emphysema is a functional obstructive disorder caused by the **loss of elastin**. Elastin is what gives the lung the feature of elastic recoil. Elastin is why a lung removed from the thorax collapses completely to a volume of zero. Elastin is how we can use our diaphragm to actively inhale, but then passively exhale. Elastin is in the greatest density **in the alveoli**. The alveoli are where air is conducted to, where gas exchange occurs, and where air is conducted from. There are 300 million alveoli, and their combined surface area is larger than that of all the other airway lumens combined. Bronchi have cartilage and aren't supposed to move. Thus, it makes sense that the things that need to inflate and deflate—the alveoli—be made of the thing that does the deflating—elastin. In emphysema, the **loss of elastin** and the **loss of the alveolar septa** are at the heart of the disease pathogenesis.

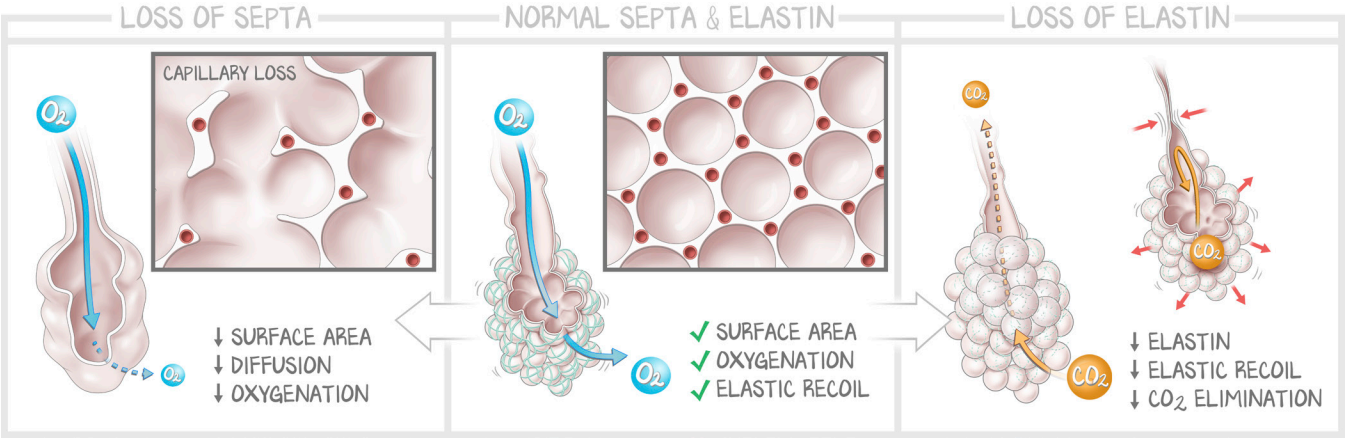
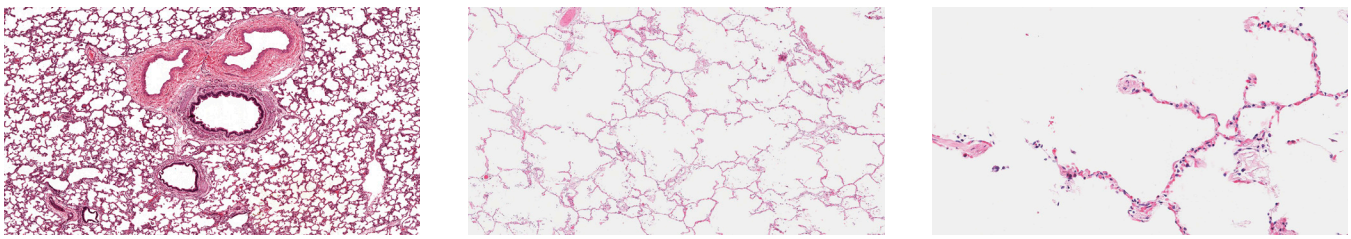


Figure 6.3: Emphysema Pathogenesis
In emphysema, there is both the loss of surface area (from the loss of the alveolar septa), which compromises the diffusion of oxygen, and the loss of elastin, which compromises air movement out of the alveoli. The loss of septa contributes to poor oxygenation and pulmonary hypertension. The loss of elastin contributes to CO_2 retention.

Think about what "loss of the septa" means at a cellular level. A septum is created when two pneumocytes come really close together. In between those two pneumocytes is an endothelial cell. Usually, the basement membrane of the endothelial cell is continuous with the neighboring pneumocyte. Where it isn't, there is a teeny tiny space where cells could go. Sometimes, alveolar macrophages go there. Usually, that space isn't there because the cells' basement membranes are glued together. To "lose a septum," there must be the loss of an endothelial cell and two pneumocytes. If they died (i.e., necrosis), there would be acute inflammation (neutrophils, macrophages, fibroblasts) and scarring of the lung (fibrosis). But histologically, emphysema does not show fibrosis in affected segments. If they underwent a coordinated, very-much-alive auto-deletion (apoptosis), there would be no acute inflammation (neutrophils, macrophages, fibroblasts) or scarring. It appears to us at OME that emphysema is likely an apoptotic process. Losing septa has two consequences. First, it vastly reduces the surface area of gas exchange. Reduced gas exchange causes both hypoxemia and hypercapnia. At rest, both oxygen and carbon dioxide are perfusion limited. **The removal of capillaries reduces overall perfusion**. Second, with fewer capillaries in parallel in the pulmonary circuit, the resistance increases, which can lead to pulmonary hypertension and heart failure.



(a) **(b)** **(c)**

Figure 6.4: Emphysema Histology
(a) Normal lung seen at low magnification, demonstrating an abundance of alveolar septa. (b) An emphysematous lung seen at low power, demonstrating how few septa there are. Both (a) and (b) are taken at 4× normal magnification. (c) A high-powered view of the emphysematous lung, demonstrating that the septa present in emphysema are normal appearing. There are fewer of them, and they have less elastin, but they otherwise look normal.

Of the septa that remain, if stained for elastin, there is an obvious, overt **loss of elastin**. Elastin is what causes the alveoli to collapse. Total collapse is a bad thing. But without elastin, there isn't any driving force for the alveoli to push out the air. Normal ventilation involves contraction of the diaphragm on

inhalation followed by relaxation of the diaphragm, letting the elastic recoil take care of exhalation. If the elastic recoil of the alveoli is lost, that doesn't happen. Air still needs to get out of the alveoli. To do that, the use of **accessory muscles** becomes necessary. Accessory muscles reduce the volume of the thorax—they **push on the alveoli**. Pushing on the alveoli pushes air out of them, which is exactly what we want to happen. Bronchi have cartilage, so the extra push from the accessory muscles doesn't do anything to them. **Bronchioles don't have cartilage**, so when those push-muscles push on the walls of the bronchioles, **their lumen gets smaller**. Smaller lumen, more resistance, less flow. Air-trapping in emphysema occurs because, in order to get the air out, the bronchioles are forced closed.

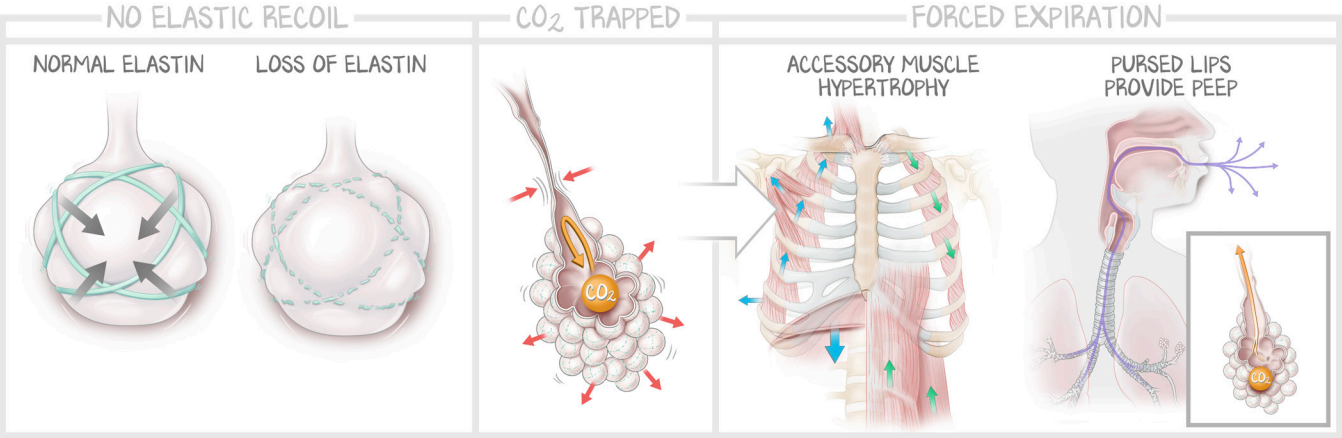


Figure 6.5: Consequence of Loss of Elastin
Schematic of the changes that accompany reduced elastin content. The presence of elastin allows for the expiration of air without the assistance of accessory muscles; the airflow out of the alveoli through the bronchioles is not hindered. As elastin is lost, more accessory muscle use is required, and the pushing force on the bronchioles leads to the airways' collapse. The forces that are necessary for expiration compromise expiration.

So that means we have two separate, likely interrelated processes that lead to one common outcome. How this happens is currently being elucidated, but we have some pretty good ideas. There are definitively two pathogenetic mechanisms—a protease-antiprotease imbalance as a result of inflammation, and oxidative stress-induced apoptosis.

Inflammation. Alveolar macrophages are there to phagocytose anything that makes it through the conducting layer. What is supposed to happen is that the conducting airways clear the air of anything other than gases. Because the system isn't perfect, a small amount of debris is going to make it to the alveoli essentially all of the time. Macrophages take care of that small amount of debris. When a person inhales cigarette smoke, a lot of debris gets to the alveoli. The pneumocytes don't like that debris and macrophages can't handle that much. They call for help by releasing inflammatory cytokines that initiate acute inflammation (neutrophils, macrophages, fibroblasts). Following smoke exposure, patients have an influx of macrophages and neutrophils into the lung. Neutrophils are implicated not only in disease initiation but also in exacerbations. These phagocytes consume the debris and release **proteases**, which help fight the "pathogens" inhaled from cigarette smoke.

Protease-Antiprotease Imbalance. Proteases degrade debris inside the air-filled spaces of alveoli. Proteases defend the alveolar cells. Antiproteases ensure those proteases don't go unchecked. A protease is an enzyme. It does what it does. And proteases cleave proteins. **Elastin is a protein.** Elastin is a protein within the connective tissue of the lung. The connective tissue is the septa. Elastin will be degraded if there is too much protease activity or too little antiprotease activity. **Protease activity goes up in patients who smoke**, the result of the acute inflammatory cells fighting the debris. Antiprotease

activity goes down in the genetic condition known as α_1-antitrypsin, discussed below. The progressive loss of elastin means a progressively increased need for the accessory muscles of expiration and the progressive worsening of the functional obstruction of the respiratory bronchiole.

Apoptosis. Oxidant stress to the pneumocytes induces the release of inflammatory cytokines. Oxidant stress may also trigger apoptosis of the pneumocytes. This is the one we're furthest from understanding, but we know it happens. Endothelial cells are sustained by VEGF, and the inhibition of VEGF in experimental models results in endothelial cell apoptosis, which in turn results in the loss of alveoli in a controlled environment without any inflammation or inflammatory cells. In this model, a gene known as RTP801, an inhibitor of mTOR, is activated. In smokers, RTP801 is also activated. Finally, a gene that comes up a lot in current research is Nrf2, which is normally degraded in the cytoplasm unless oxidant stress prevents that degradation. The purpose of Nrf2 is to initiate the transcription of protective antioxidant genes. Nothing in this paragraph was bolded because it isn't well elucidated enough to be tested on, but we thought it was interesting enough to be included.

Acinar. Every respiratory bronchiole aerates a unit of alveoli called an acinus. When patients smoke, the polluted air sees the entry to the acinus before it sees the alveoli themselves. Thus, in patients who smoke, the center of the acinus is most affected. Smoking, therefore, causes **centri-acinar emphysema**. Smoke rises, and so smoking causes **emphysema in the upper lobes**. In contrast, α_1-antitrypsin (A1AT) deficiency causes **pan-acinar** (all of the alveoli of an acinus are involved; not all of the acini of the lung are involved) **emphysema**. A1AT deficiency is a genetic defect in the synthesis of A1AT by the liver, misfolding the protein and failing to release it into circulation. A1AT is an antiprotease. Because the balance tips in favor of proteases without a noxious stimulus, all of the acinus is affected equally. A1AT is discussed in detail in Gastroenterology.

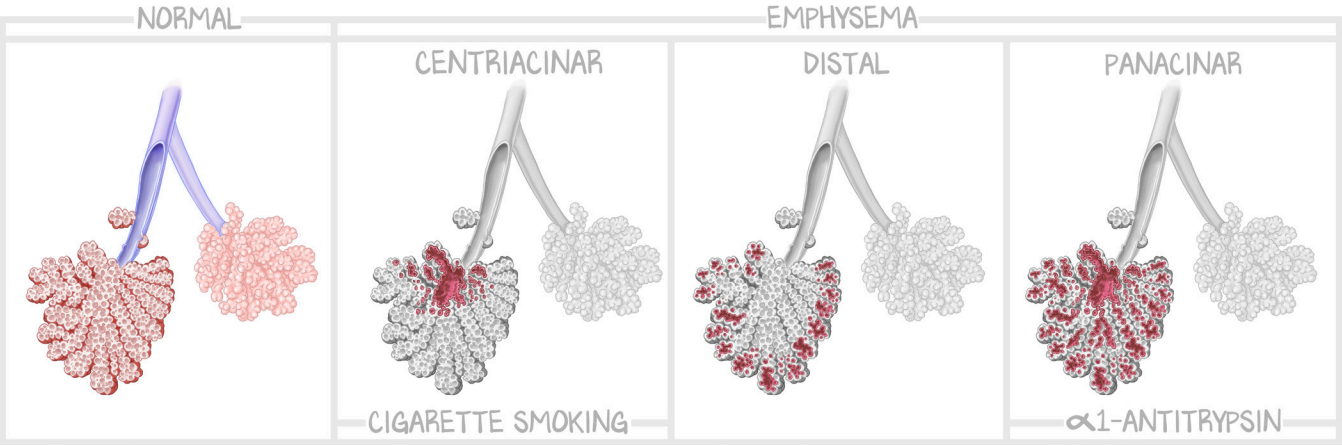


Figure 6.6: Acinar Emphysema
Schematic of the varying distribution of emphysema (loss of alveoli) based on etiology. Centriacinar emphysema occurs in the alveoli nearest the bronchioles and is associated with cigarette smoking. Distal acinar emphysema affects only the outer alveoli and spares those near the bronchioles. Do not associate any disease process with this. In panacinar emphysema, the entirety of the alveoli is affected (e.g., due to α_1-antitrypsin deficiency).

Patient presentation. In emphysema, the issue is resistance in the small airways. Resistance takes time to overcome. The **prolonged expiratory phase** allows these patients to empty their alveoli. Because the problem is collapsing bronchioles, by breathing through **pursed lips,** a small amount of backpressure is generated, which is translated onto the walls of the bronchioles, keeping them open. Backpressure sounds like resisting forward flow, which also necessitates a prolonged expiratory phase. As progressively more elastin is lost, there is a progressive demand for accessory muscle use. This active use of muscle

consumes calories and hypertrophy muscle. The **intercostal muscles hypertrophy**. As the remainder of the body reduces in weight, the AP diameter of the abdomen falls, whereas the AP diameter of the hypertrophied chest, secured by bones, remains the same. This relative loss of abdominal girth is perceived as a **barrel chest**, a perceived increase in the AP diameter of the chest. The problem with this explanation is that there is often **hyperinflation on chest X-ray**, which learners erroneously justify as the cause of the expanded chest diameter. Compared to bronchitis, **dyspnea is severe and early** in emphysema, there is usually **scant sputum production,** and **right heart failure** is rare but terminal. The absence of cyanosis, plus prolonged expiration and breathing through pursed lips, has garnered patients with this presentation of COPD the epithet of ***pink puffers***.

Asthma

The asthma discussed herein is atopic asthma, the one caused by Th2 cells, IgE, mast cells, etc., as we are about to discuss. Nonatopic asthma does exist, but atopic asthma (henceforth just 'asthma') is the disease treated with the inhalers and medications you will learn in the next lesson.

Asthma can be divided into two separate, interrelated pathologies—one that is acute and reversible, and one that is chronic and irreversible. An **acute asthma exacerbation** (an asthma attack) is an **immune-mediated process** in response to an allergen. The combination of IgE-mediated mast cell degranulation, vagal-mediated bronchoconstriction, and an exaggerated Th2 response to normally harmless environmental antigens generates bronchoconstriction, vasodilation, and mucus production that compromises the airway. **Chronic asthma**, the changes that occur to the epithelium of a person who carries the diagnosis of asthma for years, is defined by **irreversible airway remodeling**, characterized by sub-basement membrane fibrosis, hypertrophy of bronchial submucosal glands, and smooth muscle hyperplasia.

The Th2 immune response primes genetically susceptible patients to become asthmatic. The very first time an antigen is encountered, dendritic cells (the macrophages in the epithelium of the bronchi) phagocytose it, process it, and bring it back to nearby lymphoid tissue to present it to mature, naive $CD4^+$ Th0 T-helper cells. The type of antigen presented induces the Th0 cell to become a Th2 cell and release IL-4, IL-5, and IL-13. These cytokines induce B cell isotype switching to **IgE** (IL-4), the recruitment of eosinophils (IL-5), and mucus secretion (IL-13). The effects of IL-5 and IL-13 will matter more in subsequent attacks and are repeated and bolded in the paragraphs to follow. The key feature of this initial exposure is that IgE binds to **mast cells**, the Fc portion seated in the Fc receptor, ready to cross-react. The initial response primes mast cells for degranulation. This was a drive-by of the content taught in Immunology (Immunology #10: *T-cell Activation*).

The next time the patient is exposed to that antigen, the epithelium and cells of immunity are ready. Bronchoconstriction, mucosal edema, and excess mucus secretion cause the symptoms of an asthma attack.

The **early-phase reaction**—bronchoconstriction and edema—is driven by **mast cell degranulation** and **the vagus nerve**. Mast cell degranulation results from the antigen binding to IgE already planted within the membranes of the mast cells. The cross-linking of antibodies induces the release of mast cell granules. Within those granules are histamine and **leukotrienes**. Because histamine blockade has not proven to be effective in asthma management and leukotriene antagonism has, it has been postulated that **leukotrienes** are responsible for vasodilation and bronchoconstriction during the early phase. Bronchiolar constriction, aka the **bronchoconstriction** of small airways, narrows the caliber of the lumen, thereby increasing resistance to flow. There are also arteriolar changes that accompany the bronchiolar changes. Arteriolar vasodilation and the leaking of venules, resulting in tissue **edema.** Edema causes a mass effect, further limiting the caliber of the lumen airway. Separately, mediated by the vagal nerve, there is also a signal for **bronchoconstriction** through the activation of **muscarinic**

acetylcholine receptors on the smooth muscle of the bronchi. Leukotrienes and acetylcholine are clearly implicated in the pathogenesis of the disease. Edema and bronchoconstriction narrow the lumen. A narrowed lumen has greater resistance and will prevent the flow of air out of the alveoli. Patients in an asthma exacerbation present with expiratory wheezing because turbulent airflow makes noise.

The **late-phase reaction** of an acute asthma exacerbation is caused by mucus secretion. The presence of the antigen not only activates IgE on mast cells. The presence of the antigen means that dendritic cells (macrophages) engulf and present that antigen to $CD4^+$ helper T cells, just like at the beginning of the pathogenesis. That means more of the Th2 response. More IL-4, -5, and -13 are made by activated T cells. **IL-13** is responsible for the induction of **mucus secretion** by the submucosal glands, while **IL-5 recruits eosinophils**. Mucus production further obstructs airways. Eosinophils release major basic protein, which causes damage to the epithelium and sustains the inflammatory reaction. "Damage to the epithelium" results in the hallmark histologic finding of asthma exacerbations—**detachment of the epithelium.** "Sustains the inflammatory reaction" means T cells, eosinophils, and mast cells continue to be recruited and sustain the exacerbation. The cells of acute inflammation (neutrophils, macrophages, fibroblasts) may be present during an acute attack, although their role in an acute attack is minimal. Instead, those cells of acute inflammation are responsible for the chronic changes, such as subepithelial fibrosis, discussed below.

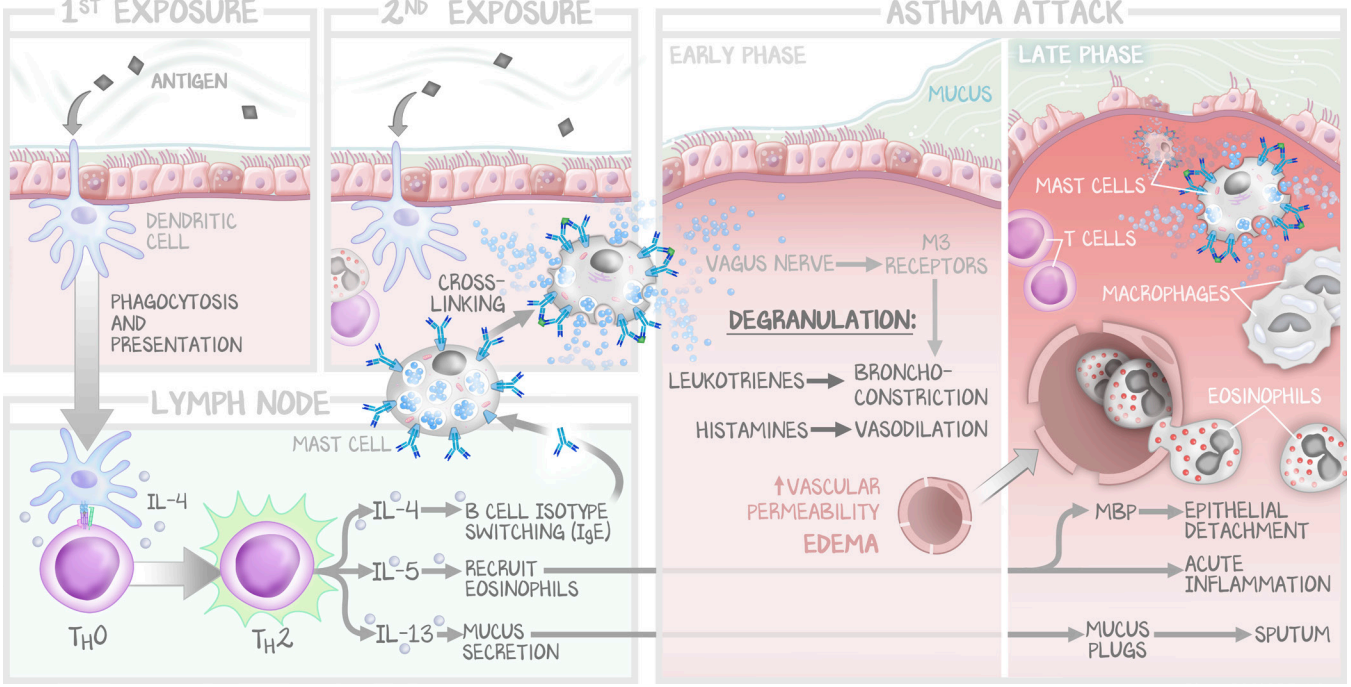


Figure 6.7: Pathogenesis of Asthma
This is a visual representation of the previous four paragraphs.

Performing an endoscopy (which compromises the lumen of the airway) during an acute asthma exacerbation (which is compromising the lumen of the airway) is generally a bad idea, so you won't get a sample of a living human's epithelium during an asthma exacerbation. However, you need to be aware of what asthma histology looks like. Especially when it comes from a **sputum sample**. Sputum samples or bronchoalveolar lavage specimens are full of **Curschmann spirals**, **eosinophils,** and **Charcot-Leyden crystals,** composed of eosinophil protein.

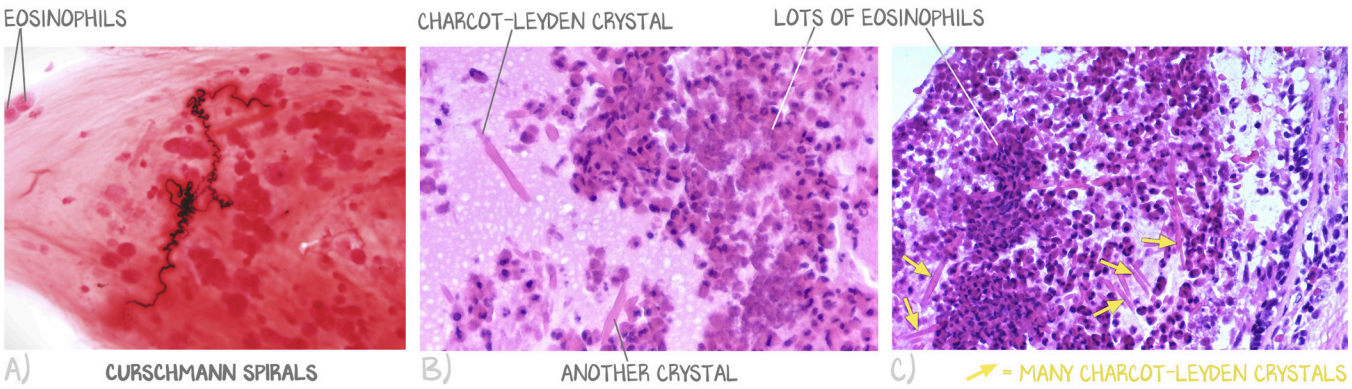


Figure 6.8: Histology of Acute Asthma Exacerbation
(a) Curschmann spirals can be found in the sputum samples of patients with acute asthma. Likely, these represent the cleared mucus plugs from the small airways. (b) Charcot-Leyden crystals and eosinophils are pathognomonic for asthma. (c) Eosinophils in the sputum are likewise helpful for the diagnosis. Eosinophils make the Charcot-Leyden crystals.

Airway remodeling. Repeated attacks result in the histology found when patients die. Patients with asthma die from a refractory asthma attack, now called acute severe asthma, formerly known as **status asthmaticus**. Airway remodeling describes the overall histologic changes. Because vasodilation is repeatedly induced, it makes sense that there is hypervascularity. Because mucus secretion is a hallmark of acute asthma, **goblet hyperplasia** and **submucosal gland hyperplasia** are expected. Because there have been sustained tonic contractions of the circumferential smooth muscle, there will be **smooth muscle hyperplasia**. And finally, because of the recurrent small number of neutrophils, macrophages, and fibroblasts, there is **subepithelial fibrosis** (collagen deposition). Over time, the accumulation of collagen from acute inflammation results in that fibrosis getting larger and larger.

Clinical course. The diagnosis is based on the demonstration of an increased obstruction to airflow (either by methacholine-induced exacerbation or β-agonist-relieved exacerbation), difficulty with exhalation (prolonged expiration, wheezing), peripheral blood eosinophilia, and the finding of eosinophils, Curschmann spirals, and Charcot-Leyden crystals in the sputum. Treatment, discussed in a separate lesson, is targeted at reducing the number of exacerbations. Moreso than in COPD, the **treatment of asthma is anti-inflammatory.** Targeting the disease pathogenesis—macrophages, Th2 cells, and eosinophils—prevents exacerbations. During exacerbations, relief from symptoms comes from the manipulation of mucus secretion and bronchodilation. In the usual case, with intervals of freedom from respiratory difficulty, the disease is more discouraging and disabling than lethal, and most individuals with asthma have a normal life expectancy. Many cases of childhood asthma simply spontaneously improve with age.

Citations

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